Substituent Effects in Chain-Breaking Aryltellurophenol Antioxidants

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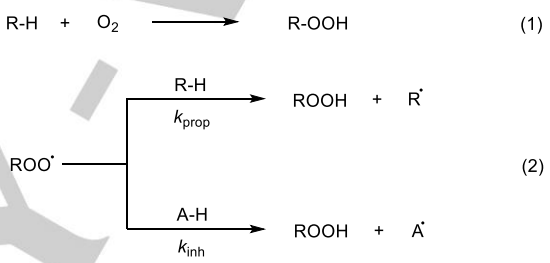
Abstract: 2-Aryltellurophenols substituted in the aryltelluro or phenolic part of the molecule were prepared by lithiation of the corresponding THP-protected 2-bromophenol, followed by reaction with a suitable diaryl ditelluride and deprotection. In a two-phase system containing *N*-acetylcysteine as a co-antioxidant in the aqueous phase, all compounds quenched lipid peroxyl radicals more efficiently than α-tocopherol with 3 to 5-fold longer inhibition times. Thus, they offer better and longer lasting antioxidant protection than alkyltellurophenols recently prepared. Compounds carrying electron donating *para*-substituents in the aryltelluro (**9a**) or phenolic (**12c**) part of the molecule showed the best results. The mechanism for quenching of peroxyl radicals was considered and discussed in the light of calculated OH bond dissociation energies, deuterium labelling experiments and studies of thiol-consumption in the aqueous phase.

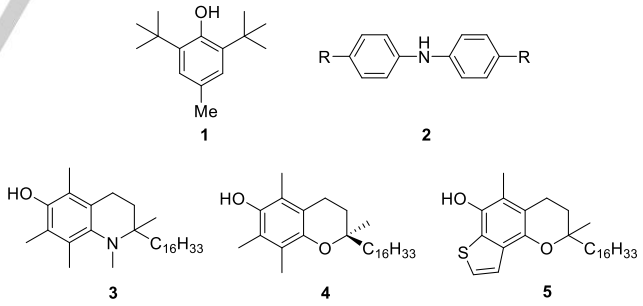
Introduction

In the presence of atmospheric oxygen, all organic materials (R-H) undergo autoxidation. This is a free radical chain reaction resulting in the formation of organic hydroperoxides ROOH (eq. 1). The most successful way to slow down the rate of autoxidation has been to add small amounts of a radical-trapping antioxidant A-H, capable of quenching intermediate peroxyl radicals with a rate constant k_{inh} significantly larger than the rate of propagation, k_{prop} (eq. 2). The rubber, plastics and food/feed industries are the largest consumers of antioxidants and they traditionally use small amounts of sterically hindered phenols (such as BHT (**1**)) and aromatic amines (for example 4,4'-dialkyldiphenylamines **2**) as additives to stabilize their products.[1]

Since the 1950s, considerable work has been done in order to improve the reactivity (k_{inh} in eq. 2) of phenolic compounds.[2,3] Briefly, electron-donating substituents in the phenol were found to cause an increase in k_{inh} while electron withdrawing ones had the opposite effect.[4] Also, the significance of stereoelectronic



factors was recognized.[5] For example, for a *para*-methoxy group to lower the bond dissociation energy of the OH-group (BDE_{O-H}) and increase the rate of H-atom transfer, it has to adopt a conformation where an oxygen lone-pair can overlap with the aromatic π-electron system.



The strategy to increase k_{inh} by introduction of electron donating groups will only be successful as long as the ionization potential of the antioxidant does not drop below the point where direct electron transfer to atmospheric oxygen occurs. Shortly after the millennium, Pratt, Valgimigli and Porter presented a solution to this problem. They found that replacement of C with N at the 3- or/and 5-positions in a phenol significantly increased the oxidation potential of the resulting pyridinols[6]/pyrimidinols[7] while the BDE_{O-H} increased only marginally. Based on this finding, naphthyridinol **3**[8] and more readily available analogues thereof[9] were prepared. The novel antioxidants were more than ten-fold more reactive than α-tocopherol (**4**; $k_{inh} = 3.2 \times 10^6$ $M^{-1}s^{-1}$) towards peroxyl radicals.

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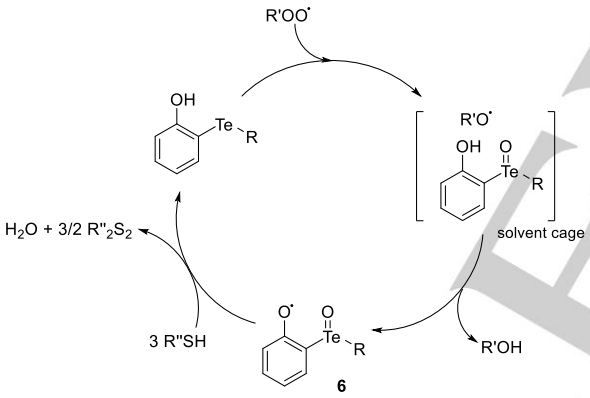
Amorati and co-workers[10] recently reported that tocopherol analogue **5**, carrying a benzannulated thiophene moiety, was 3-fold more reactive than α-tocopherol as a radical-trapping agent. It was proposed that the observed rate acceleration was due to a stabilizing, non-covalent, sulfur···oxygen σ-hole interaction in the phenoxyl radical corresponding to **5**.

We have found a conceptually different way to improve the radical-trapping activity of phenols. The seminal observation we made some time ago was that alkyltellurophenols could quench lipid peroxyl radicals with a $k_{inh} > 10^7$ M^{-1} s^{-1}.[11] Since the rate constant for reaction of phenol itself with peroxyl radicals is only in the order of 10^3 M^{-1} s^{-1}, we have proposed an unconventional mechanism for the reaction, involving O-atom transfer from peroxyl radical to tellurium, followed by H-atom transfer from phenol to the resulting alkoxyl radical (Scheme 1). In the presence of thiols or other mild reducing agents the alkyltellurophenol could be regenerated from the telluroxide/phenoxyl radical **6** to allow for a catalytic mechanism.[12] It is noteworthy that the incoming peroxyl radical ROO$^{\bullet}$ is reduced all the way to an alcohol ROH in the process, thus obviating the need for an additional peroxide decomposing antioxidant.

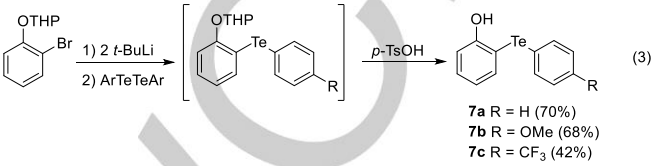


Scheme 1. Proposed mechanism for the reduction of peroxyl radicals to alcohols by alkyltellurophenols in the presence of thiol.

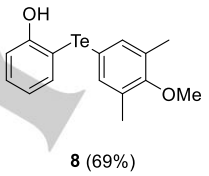
In order to improve the reactivity and regenerability of our antioxidants we were curious to study substituent effects, both in the alkyltelluro- and phenolic parts of the molecule. Towards this end, we decided to change the alkyl group for an aryl in order to conveniently vary the electron density at the heteroatom by the proper choice of *para*-substituent. Described in the following are the preparation of such compounds as well as reports on their reactivities and regenerability in a two-phase lipid peroxidation system.

Results and Discussion

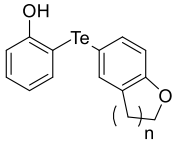
Synthesis. Aryltellurophenols **7**, carrying electron donating or electron withdrawing groups in the aryl moiety, were prepared in moderate yields (42-70%) by lithiation of THP-protected 2-bromophenol followed by reaction with the appropriate diaryl ditelluride and deprotection of the crude product in CH_3OH/CH_2Cl_2 containing *p*-TsOH (eq. 3). A more straight-forward procedure, involving lithiation of 2-bromphenol with 3 equivalents of *t*-BuLi and reaction with a ditelluride, produced **7** in considerably lower yields (< 15%).



Compounds **8** and **9a**-**b** were obtained using a similar protocol. For stereoelectronic reasons, the *p*-methoxy group in **8** was expected to be less electron donating than the one in **7b**. On the contrary, the *p*-alkoxy groups in **9** are oriented in such a way that the electron density at tellurium would be epected to be higher than in **7b**.

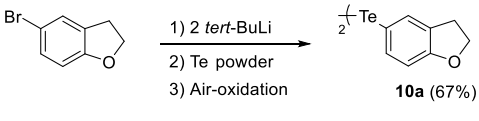


8 (69%)

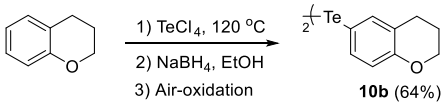


9a n = 1 (75%)
9b n = 2 (80%)

The diaryl ditellurides **10a-b** required for the preparation of **9a-b** were conveniently accessed either via lithium-halogen exchange followed by reaction with tellurium powder and air-oxidation (eq. 4) or by electrophilic aromatic substitution using tellurium tetrachloride as a source of the active electrophile. Borohydride reduction of the aryltellurium trichloride produced, followed by air-oxidation of the corresponding arenetellurolate, provided the desired ditelluride (eq. 5).

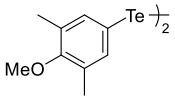


10a (67%) (4)



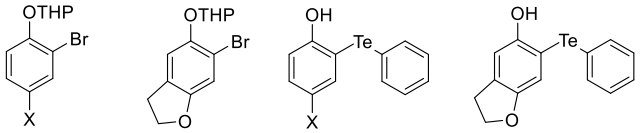
10b (64%) (5)

Compound **10c**, required to make **8**, was obtained in good yield (89%) following the procedure used for the preparation of **10a**.



10c (89%)

In order to study substituent effects in the phenolic part of the molecule, electron donating and electron withdrawing substituents were introduced *para* to the OH in compound **7a**. Following literature procedures, THP-protected bromophenols **11a-b** and **11c** were prepared and subjected to the reaction conditions shown in equation 3. The corresponding phenyltellurophenols **12a-c** were obtained in 40, 65 and 29% yields, respectively.



11a X = OMe **11b** X = CF_3 **11c** **12a** X = OMe (40%) **12b** X = CF_3 (65%) **12c** (29%)

Evaluation. The radical-trapping capacity and regenerability of the novel aryltellurophenols prepared were evaluated in a water/chlorobenzene two-phase system where peroxidation of linoleic acid (36.2 mM), initiated by an azo-initiator (2,2'-azobis-2,4-dimethylvaleronitrile, 1.4 mM) and inhibited by the antioxidant (40 μM), was on-going in the organic phase.[12] *N*-acetylcysteine (NAC, 1.0 mM) as a co-antioxidant was present in the aqueous layer to serve as a regenerating agent for the antioxidant. The chlorobenzene layer was sampled every 20 minutes and analyzed by HPLC for conjugated diene (λ_{max} = 234 nm) formed as a result of peroxidation of the fatty acid in the presence of dioxygen. By monitoring the concentration of conjugated diene with time, the rate of peroxidation during the inhibited phase (R_{inh}) and the inhibition time (T_{inh}) could be determined and benchmarked against α-tocopherol (Figure 1). Whether or not NAC was present in the aqueous phase, α-tocopherol could inhibit peroxidation for ca. 100 min with an R_{inh} of 25 μM/h. When it was all consumed, the rate of peroxidation increased considerably to a value corresponding to uninhibited peroxidation. Thus, α-tocopherol is not regenerable under the conditions of the assay.

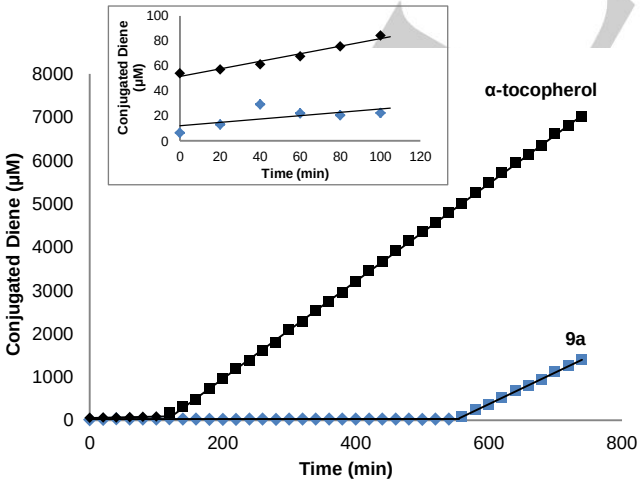


Figure 1. Peroxidation traces (conjugated diene vs time) recorded with compound **9a** and α-tocopherol. Initial part (100 min) of the peroxidation trace is magnified.

Maximal antioxidant activity for the organotellurium compounds was seen only in the presence of aqueous-phase NAC (Table 1). In the absence of the co-antioxidant, no inhibition (**7a**, **7c**, **8,** **12b**) or short inhibition (**7b**, **9a**, **9b** and **12a**) was usually seen with 14 < T_{inh} < 74 min and R_{inh}-values > 38 μM/h. Only compound **12c** showed a longer T_{inh} (136 min) and a shorter R_{inh} (23 μM/h) than α-tocopherol under thiol-free conditions. The organotellurium compounds are readily oxidized by the small amounts of linoleic acid hydroperoxide which are always present in the commercial sample of linoleic acid and the telluroxides thus formed can only inhibit peroxidation by hydrogen atom transfer. It may be that some remaining **12c** and the corresponding telluroxide are responsible for the good antioxidant activity provided by this compound in the absence of NAC.

Table 1. Inhibition Rates of Conjugated Diene Formation (R_{inh}) and Inhibition Times (T_{inh}) in the Presence and Absence of NAC (1.0 mM) in the Two-Phase Model

Antioxidant (40 μM)	with NAC		without NAC	
	R_{inh}[a] (μM/h)	T_{inh}[b] (min)	R_{inh}[a] (μM/h)	T_{inh}[b] (min)
4	25 ± 1	97 ± 5	28 ± 2	109 ± 9
7a	4 ± 1	325 ± 8	556	0
7b	0.7 ± 0.7	379 ± 3	69	42
7c	15 ± 4	310 ± 9	565	0
8	5 ± 1	349 ± 9	633	0
9a	0.4 ± 0	571 ± 3	77	34
9b	0.9 ± 0.8	363 ± 10	69	14
12a	1 ± 0.6	403 ± 6	38	74
12b	9 ± 1	282 ± 9	385	0
12c	0.3 ± 0.3	609 ± 9	23 ± 1	136 ± 6

[a] Rate of peroxidation during the inhibited phase (uninhibited rate ca. 592 μM/h). Errors correspond to ± SD for triplicates. [b] Inhibited phase of peroxidation. Reactions were monitored for 740 min. Errors correspond to ± SD for triplicates.

In the presence of NAC, all compounds outperformed α-tocopherol when it comes to inhibited rate of peroxidation (0.3 < R_{inh} < 15 μM/h). Judging from the R_{inh}-values recorded, compounds **9a** and **12c** inhibited peroxidation 63- and 83-fold, respectively, more efficiently than α-tocopherol. Concerning substituent effects in the aryltelluro moiety, the trend is that electron donating substituents improve reactivity (**7b** > **7a** > **7c**). Among the compounds carrying an oxygen substituent *para* to tellurium, reactivities increase as the overlap between the oxygen lone-pair and the aromatic π-system is improved (**8** < **7b** ≈ **9b** < **9a**). Electron donating *para*-substituents in the phenolic moiety cause a rate increase in the quenching of peroxyl radicals (**12b** < **7a** < **12a** < **12c**).

In the presence of NAC, all compounds inhibited peroxidation for longer than α-tocopherol (282 < T_{inh} < 609 min). Largely, the substituent effects seen for R_{inh} were reflected in T_{inh}, but the values did not vary so much. Thus, compounds with electron donating *para*-substituents either in the aryltelluro (**9a**; T_{inh} = 571 min, see Figure 1) or in the phenolic (**12c**; T_{inh} = 609 min) part of the molecule offered the most long-lasting antioxidant protection.

Thiol-consumption in the aqueous phase during normal peroxidation conditions was monitored by a procedure recently reported.[13] In brief, the aqueous phase was sampled every 30 min and the remaining NAC was allowed to react with Aldrithiol-4®. 4-Mercaptopyridine formed in the thiol exchange reaction was detected spectrophotometrically at 324 nm and used as a measure of the NAC-concentration. For antioxidants that did not utilize NAC for regeneration (α-tocopherol; 33 ± 4 μM/h), the rate of thiol consumption was roughly the same as in a control experiment without any antioxidant (37 ± 8 μM/h). In the presence of tellurium-based antioxidants, a significant increase in the rate of NAC-consumption was observed (Table 2). Roughly, thiol-consumption is inversely related to the inhibition time, T_{inh}. Extrapolation in the NAC-concentration vs time plots showed that the aqueous phase was depleted of thiol only shortly after T_{inh}. It therefore seems that the limiting factor for the duration of antioxidant protection is the availability of thiol.

Table 2. NAC-Consumption in the Aqueous Phase during Peroxidation Inhibited by Aryltellurophenols

Antioxidant (40 μM)	NAC-Consumption Rate[a] (μM/h)	Antioxidant (40 μM)	NAC-Consumption Rate[a] (μM/h)
4	33 ± 4	**9a**	105 ± 6
7a	153 ± 4	**9b**	149 ± 3
7b	153 ± 4	**12a**	144 ± 2
7c	155 ± 2	**12b**	158 ± 11
8	152 ± 11	**12c**	104 ± 10

[a] Errors correspond to ± SD for triplicates. NAC-consumption rate for sample without antioxidant is 37 ± 8 μM/h and sample containing only NAC is 27 ± 5 μM/h.

Computational studies. In order to rationalize the observed substituent effects in the aryltelluro and phenolic parts of the aryltellurophenols, BDE_{O-H}-calculations were performed for compounds **7**, **8**, **9** and **12** as well as their corresponding telluroxides (Table 3). The geometries of tellurides, telluroxides and their respective phenoxyl radicals were optimized at the M05-2X/def2-SVP level[14] with Gaussian09 Rev. E.01.[15] Single-point energies were calculated with the M05-2X/def2 TZVPP using the default continuum solvation method and benzene as the solvent. This was done to match typical conditions for experimentally determined BDEs. The method was benchmarked against a series of reference compounds with a mean deviation of -0.4 kcal/mol and a mean absolute deviation of 0.8 kcal/mol (see Supporting Information). As previously found for methyltellurophenols 2-HO-C_6H_4-TeMe,[16] tellurides prefer a conformation where the OH is hydrogen bonded to Te and the dihedral angle between the phenolic ring and the Ar-Te-bond is close to 90°. On the other hand, the corresponding phenoxyl radicals adopt a conformation where this angle is close to 0°. As shown in Table 3, the BDE_{O-H} for compounds **7**, **8**, and **9** and their respective telluroxides are practically invariant to substitution in the aryltelluro moiety (84.6-85.8 kcal/mol for tellurides and 96.9-97.7 kcal/mol for telluroxides). On the other hand, the substituents in the phenolic part of the molecule clearly affect the BDE_{O-H} both in the tellurides (**7a** and **12**) and the corresponding telluroxides (77.9-87.2 kcal/mol for tellurides and 88.5-101.5 kcal/mol for telluroxides).

Table 3. Calculated BDE_{O-H}s in kcal/mol for telluride, Te(II), and telluroxide, Te(IV), forms of antioxidants at the M05-2X/def2-TZVPP level with benzene continuum solvation with geometries optimized at M05-2X/def2-SVP

Antioxidant (40 μM)	BDE_{O-H} (kcal/mol)		Antioxidant (40 μM)	BDE_{O-H} (kcal/mol)	
	Te (II)[a]	Te (IV)		Te (II)	Te (IV)
7a	85.2	97.1	**9b**	85.1	97.7
7b	84.6	97.4	**12a**	79.5	89.9
7c	85.8	96.9	**12b**	87.2	101.5
8	84.9	97.0	**12c**	77.9	88.5
9a	85.0	97.7			

[a] The calculated BDE_{O-H} for α-tocopherol with the phytyl chain replaced by a methyl was 77.1 kcal/mol.

Deuterium labelling experiments. In order to find out more about the mechanism for quenching of peroxyl radicals, we prepared the *O*-deuterated analog **12c-D** of **12c** by sodium hydride deprotonation in $CDCl_3$, followed by addition of DCl. To avoid H for D exchange, the compound was tested in the two-phase model in the absence of NAC and using D_2O instead of water in the aqueous phase. As shown in Table 4, the observed R_{inh} for **12c-D** was considerably higher (131 μM/h) than recorded for **12c** in H_2O (23 μM/h). Control experiments with **12c**/D_2O as well as **12c-D**/H_2O showed that H for D and D for H exchange occurred rapidly in the two-phase model. Thus, **12c** was a much poorer quencher of peroxyl radicals when tested with D_2O and **12c-D** performed much better when tested with H_2O (Table 4). The observed isotope effect indicates that H-atom transfer would

Table 4. Inhibition Rates of Conjugated Diene Formation (R_{inh}) and Inhibition Times (T_{inh}) for Compounds **12c** and **12c-D** with H_2O and D_2O

Antioxidant (40 μM)	with H_2O		with D_2O	
	R_{inh}[a] (μM/h)	T_{inh}[b] (min)	R_{inh}[a] (μM/h)	T_{inh}[b] (min)
12c	23 ± 1	136 ± 6	92 ± 2	109 ± 1
12c-D	28 ± 2	135 ± 2	131 ± 3	102 ± 3

[a] Rate of peroxidation during the inhibited phase (uninhibited rate ca. 592 μM/h). Errors correspond to ± SD for triplicates. [b] Inhibited phase of peroxidation. Errors correspond to ± SD for triplicates.

be the rate-limiting step in the antioxidant mechanism (see Scheme 1) for **12c**.

Mechanistic Considerations. The proposed mechanism for the catalytic chain-breaking activity of alkyltellurophenols is shown in Scheme 1. It is our belief that aryltellurophenols react in an analogous manner. We observe in this study that electron donating substituents in the phenolic part of the 2-aryltelluro phenols cause a weakening of the OH bond and an increase in the reactivity towards peroxyl radicals. Furthermore, the results with **12c-D** suggest that H-atom transfer is involved in the slowest step of the quenching mechanism. If so, according to the mechanistic proposal in Scheme 1, one would expect a good correlation of log(1/R_{inh}) and the BDE_{O-H} for the telluroxides of compounds **7a** and **12a**-**c**. This is indeed what we observe (Figure 2). Also, a good correlation of log(1/R_{inh}) with the Hammett parameters for H, OMe and CF_3 was seen (see Supporting Information).

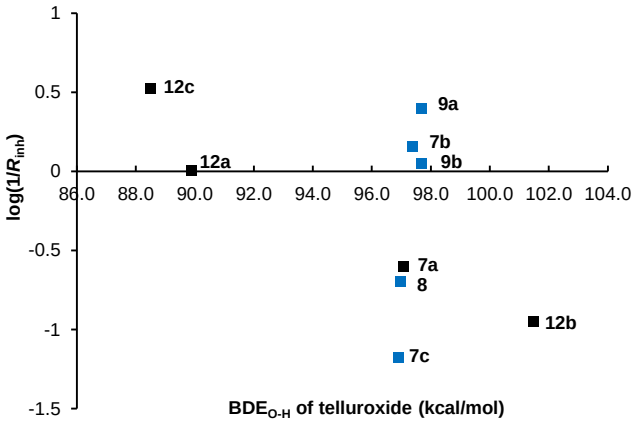


Figure 2. BDE_{O-H} of telluroxide vs log(1/R_{inh}). The series **7a**, **12a**-**c** represent variation of the substituent in the phenolic part (black), while the series **7a**-**c** and **9a**-**b** represent variation of the substituent in the aryltelluro part.

The BDE_{O-H} for the telluroxides of compounds substituted in the aryltelluro moiety (**7b**, **7c**, **8** and **9**) on the other hand are practically identical. However, there are large variations in the reactivities of these compounds. Electron donating groups cause an increase in the quenching capacity and electron withdrawing ones have the opposite effect. This is consistent with a good correlation of log(1/R_{inh}) with the Hammett parameters for H, OMe and CF_3, although only three points could be used (see Supporting Information). Figure 2 seems to indicate that a change in mechanism or in the rate-limiting step of the mechanism for the quenching reaction occurs when the *para*-substituents in the phenolic and aryltelluro groups are varied. As suggested by one reviewer, it could be that the oxygen transfer mechanism comes into play only when the electron density at tellurium is high enough (compounds **7b**, **9a** and **9b**) and the other compounds react by conventional H-atom transfer. In fact, all other compounds have a fairly linear relationship between BDE_{O-H} of tellurides and log(1/R_{inh}). The only problem here is the high reactivity of these componds towards peroxyl radicals. It is much higher than expected for phenols carrying an *ortho*-aryltelluro group and additional substituents.

O-atom transfer from a peroxyl radical to tellurium and H-atom transfer from a phenol to an alkoxyl radical in a solvent cage are both facile processes. It may be that the activation energies for these processes are quite similar. This could possibly explain the observed substituent effects on reactivity for the aryltellurophenols and the deuterium isotope effect for compound **12c**.

Conclusions

All aryltellurophenol antioxidants described in this paper outperform α-tocopherol when it comes to radical trapping activity and inhibition time. They also offer a better and longer lasting antioxidant protection than alkyltellurophenols previously described.[12d] Since the BDE_{O-H} in aryltellurophenols is often significantly larger than recorded for α-tocopherol, they are unlikely to quench peroxyl radicals by a conventional mechanism involving formal H-atom transfer from phenol to peroxyl radical. We have instead proposed a two-step mechanism for the quenching reaction involving O-atom transfer to tellurium, followed by H-atom transfer from phenol to alkoxyl radical. Deuterium labelling experiments suggested that H-atom transfer could be the slow and rate-limiting step and the reactivity of compounds substituted in the phenolic part of the molecule correlated well with the BDE_{O-H} for the corresponding telluroxides. Rate-enhancement was also observed with compounds carrying electron donating substituents in the aryltelluro moiety.

The observed substituent dependence on reactivity was largely reflected also in the inhibition times. Electron donating substituents in the phenolic or aryltelluro moieties caused an increase in T_{inh} while electron withdrawing groups had the opposite effect.

Availability of thiol in the aqueous phase is a requirement for the catalytic action of the organotellurium antioxidants. When all thiol is consumed, peroxidation increases rapidly. The trend that the most reactive antioxidants consumed thiol at a slower rate could be rationalized in terms of a solvent cage where O- and H-atom transfer is occurring (Scheme 1). If H-atoms are not transferred quickly enough, alkoxyl radicals would leak out of the cage and initiate new chain reactions. Whenever this happens, thiol would be consumed and wasted in the regeneration of the organotellurium antioxidant.

With some exceptions,[17] most antioxidants used today for the stabilization of man-made and natural materials act on a stoichiometric basis. Thus, each molecule of a phenol or aromatic amine additive can at most quench two peroxyl radicals before it is all consumed. It would be more sustainable and atom-efficient to regenerate the valuable antioxidant with some

cheap co-antioxidant and enable quenching of multiple peroxyl radicals. This is exactly what our aryltellurophenols do. Provided that they do not show any alarming toxicity or undesired redox activity, they could therefore be considered as "green" antioxidants. The fact that tellurium is bonded to two aryl moieties is likely to make the compounds less prone to degradation in vivo to form more toxic inorganic tellurium species. Since thiols function as co-antioxidants in biological systems (glutathione) one may even consider drug applications of our antioxidants, for example to relieve oxidative stress. Since aryltellurophenols react readily with hydroperoxides and the resulting telluroxides are easily reduced by thiols our compounds are also expected to show hydroperoxide-decomposing antioxidant activity, mimicking the action of the glutathione peroxidase enzymes.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on 300 MHz (^{1}H: 300 MHz; ^{13}C: 75 MHz), 400 MHz (^{1}H: 399.97 MHz; ^{13}C 100.58 MHz) and 500 MHz (^{1}H: 499.93 MHz; ^{13}C: 125.70 MHz) spectrometers, using the residual solvent peaks of $CDCl_3$ (^{1}H: δ = 7.26; ^{13}C: δ = 77.0) as an indirect reference to TMS. ^{125}Te NMR spectra were recorded on a 400 MHz spectrometer (^{125}Te: 126.19 MHz) using Ph_2Te_2 (δ = 423ppm) as external standard. ^{19}F-NMR spectra were recorded on a 400 MHz spectrometer (^{19}F: 376 MHz) using $CFCl_3$ (δ = 0.0 ppm) as external standard. The melting points are uncorrected. Flash column chromatography was performed using silica gel (0.04-0.06 mm). Tetrahydrofuran was dried in a solvent purification system by passing it through an activated alumina column. Chroman,[18] 5-bromo-2,3-dihydrobenzofuran,[19] *O*-THP-6-bromo-2,3-dihydrobenzofuran-5-ol,[19,20] *O*-THP-2-bromophenol,[21] *O*-THP-2-bromo-4-methoxyphenol,[21] 5-bromo-2-methoxy-1,3-dimethylbenzene,[22] 2-bromo-4-(trifluoromethyl)phenol,[23] diphenyl ditelluride,[24] bis(4-methoxyphenyl) ditelluride[25] and bis(4-trifluoromethylphenyl) ditelluride[26] were prepared according to literature procedures.

General procedure: Synthesis of 2-(aryltelluro) phenols

To a solution of THP-protected 2-bromophenol derivate (1.0 equiv.) in anhydrous THF at -78 °C under nitrogen was added *tert*-butyllithium (1.7 M, 2.0 equiv.). After stirring for 1 hour at -78 °C, diaryl ditelluride (1.0 equiv.) was added and the reaction was allowed to stir for overnight. The reaction mixture was quenched with a saturated ammonium chloride solution (20 mL) and extracted with diethyl ether (30 mL × 3). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. To a solution of the crude mixture in methanol (10 mL) and dichloromethane (10 mL) was added *p*-toluensulfonic acid monohydrate (18 mol%) under nitrogen. After stirring for 4 hours, the reaction mixture was quenched with a saturated aqueous solution of sodium hydrogen carbonate (10 mL) and extracted with diethyl ether (30 mL × 3). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography to give the title compound.

2-(Phenyltelluro)phenol (**7a**). *O*-THP-2-bromophenol (257 mg, 1.0 mmol), *tert*-butyllithium (1.7 M, 1.2 mL, 2.0 mmol), diphenyl ditelluride (409 mg, 1.0 mmol), *p*-toluensulfonic acid monohydrate (35 mg, 0.18 mmol) were reacted according to general procedure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 97.5:2.5 to 95:5) to give the title compound as a yellow solid (210 mg, 70%). M.p. 33-35 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.51 (m, 2H), 7.35 (td, *J* = 1.6, 7.6 Hz, 1H), 7.24 (m, 1H), 7.18 (m, 2H), 7.09 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.82 (m, 1H), 6.15 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 141.7, 135.9, 132.4, 129.7, 127.8, 121.8, 113.9, 113.8, 103.7. ^{125}Te NMR (126 MHz, $CDCl_3$): δ = 425. ^{1}H and ^{13}C were in accord with the literature.[27]

2-[(4-Methoxyphenyl)tellullro]phenol (**7b**). *O*-THP-2-bromophenol (342 mg, 1.3 mmol), *tert*-butyllithium (1.7 M, 1.5 mL, 2.6 mmol), bis-4-(methoxy)phenyl ditelluride (626 mg, 1.3 mmol), *p*-toluensulfonic acid monohydrate (45 mg, 0.24 mmol) were reacted according to general procedure to give the title compound as an orange solid (288 mg, 68%). M.p. 79-82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.54 (m, 2H), 7.28 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.02 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.74-6.80 (several peaks, 3H), 6.10 (s, 1H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.8, 156.8, 140.1, 139.2, 131.4, 121.7, 115.6, 113.8, 104.7, 102.3, 55.0. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 443. HRMS (TOF MS EI$^+$) m/z calcd for $C_{13}H_{12}O_2Te$ [M]$^+$: 329.9900. Found: 329.9906.

2-[(4-(Trifluoromethyl)phenyl)telluro]phenol (**7c**). *O*-THP-2-bromophenol (237 mg, 0.92 mmol), *tert*-butyllithium (1.7 M, 1.1 mL, 1.8 mmol), bis-4-(trifluoromethyl)phenyl ditelluride (500 mg, 0.92 mmol), *p*-toluensulfonic acid monohydrate (32 mg, 0.17 mmol) were reacted according to the general procedure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 93:7) to give the title compound as a yellow oil (141 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.55-7.53 (several peaks, 2H), 7.38-7.42 (several peaks, 3H), 7.14 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 6.87 (td, *J* = 7.2 Hz, 1.2 Hz, 1H), 6.11(s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.6, 142.0, 135.1, 133.0, 129.8 (q, *J* = 33 Hz), 126.1 (q, *J* = 3.8 Hz, 124.0 (q, *J* = 270 Hz), 122.1, 119.6 (q, *J* = 1.5 Hz), 114.3, 102.9. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 442. ^{19}F NMR (376 MHz, $CDCl_3$) δ = 62.9. HRMS (TOF MS EI$^+$) m/z calcd for $C_{13}H_9F_3OTe$ [M]$^+$: 367.9668. Found: 367.9673.

2-[(4-Methoxy-3,5-dimethylphenyl)telluro]phenol (**8**). *O*-THP-2-bromophenol (257 mg, 1.0 mmol), *tert*-butyllithium (1.7 M, 1.2 mL, 2.0 mmol), bis(4-methoxy-3,5-dimethylphenyl) ditelluride (526 mg, 1.0 mmol), *p*-toluensulfonic acid monohydrate (35 mg, 0.19 mmol) were reacted according to general procedure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 93:7) to give the title compound as a yellow oil (245 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.31 (m, 1H), 7.25 (s, 2H), 7.05 (dd, *J* = 0.8, 8.0 Hz, 1H), 6.80 (m, 1H), 6.21 (s, 1H), 3.69 (s, 3H), 2.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.3, 157.2, 141.1, 137.5, 132.6, 131.9, 121.7, 113.8, 107.0, 104.2, 59.7, 15.8. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 421. HRMS (TOF MS EI$^+$) m/z calcd for $C_{15}H_{16}O_2Te$ [M]$^+$: 358.0213. Found: 358.0218.

2-[(2,3-Dihydrobenzofuran-5-yl)telluro]phenol (**9a**). *O*-THP-2-bromophenol (257 mg, 1.0 mmol), *tert*-butyllithium (1.7 M, 1.2 mL, 2.0 mmol), bis(2,3-dihydrobenzofuran-5-yl) ditelluride (493 mg, 1.0 mmol), *p*-toluensulfonic acid monohydrate (35 mg, 0.18 mmol) were reacted according to general procedure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 95:5 to 93:7) to give the title compound as a yellow solid (254 mg, 75%). M.p. 91-93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (dd, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 7.43 (dd, *J* = 8.0 Hz, 0.8 Hz,1H), 7.28 (m, 1H), 7.02 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 6.78 (td, *J* = 7.2 Hz, 1.2 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.13 (s, 1H), 4.54 (t, *J* = 8.8 Hz, 2H), 3.15 (t, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.6, 157.0, 140.5, 138.1, 134.7, 131.6, 129.3, 121.7, 113.8, 111.0, 104.8, 101.6, 71.3, 29.4. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 440. HRMS (TOF MS EI$^+$) m/z calcd for $C_{14}H_{12}O_2Te$ [M]$^+$: 341.9900. Found: 341.9901.

2-(Chroman-6-yltelluro)phenol (**9b**). *O*-THP-2-bromophenol (232 mg, 0.9 mmol), *tert*-butyllithium (1.7 M, 1.1 mL, 1.8 mmol), bis(chroman-6-yl) ditelluride (470 mg, 0.9 mmol), *p*-toluensulfonic acid monohydrate (32 mg, 0.17 mmol) were reacted according to general procedure to give the title compound as a yellow solid (255 mg, 80%). M.p. 60-62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.35-7.38 (several peaks, 2H), 7.31 (m, 1H), 7.02 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.78 (dd, *J* = 1.2, 7.6 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.19 (s, 1H), 4.16 (m, 2H), 2.71 (t, *J* = 6.8 Hz, 2H), 1.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.0, 155.4, 140.6, 139.4, 136.9, 131.6, 124.1, 121.6, 118.4, 113.8, 104.6, 101.6, 66.4, 24.6, 21.9. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 434. HRMS (TOF MS EI$^+$) m/z calcd for $C_{15}H_{14}O_2Te$ [M]$^+$: 356.0056. Found: 356.0059.

Bis(2,3-Dihydrobenzofuran-5-yl) Ditelluride (**10a**). To a solution of 5-bromo-2,3-dihydrobenzofuran in anhydrous THF (15 mL) at -78 °C under nitrogen was added *tert*-butyllithium (1.7 M, 3.7 mL, 6.3 mmol). The solution was stirred for 1 hour at -78 °C prior to the addition of freshly ground tellurium powder (406 mg, 3.2 mmol). After stirring for 2 hours at ambient temperature, the solution was quenched with a saturated ammonium chloride solution (10 mL) and extracted with diethyl ether (20 mL × 3). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pentane/ethyl acetate = 95:5) to give the title compound as a deep red solid (525 mg, 67%). M.p. 111-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 0.8 Hz, 2H), 7.51 (m, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 4.57 (t, *J* = 8.4 Hz, 4H), 3.17 (t, *J* = 8.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.9, 139.3, 135.9, 128.6, 110.4, 97.1, 71.3, 29.3. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 517. HRMS (TOF MS EI$^+$) m/z calcd for $C_{16}H_{14}O_2Te_2$ [M]$^+$: 497.9118. Found: 497.9125.

Bis(Chroman-6-yl) Ditelluride (**10b**). Chroman (402 mg, 3.0 mmol) was added to tellurium tetrachloride (790 mg, 3.0 mmol) at 120 °C under nitrogen. The reaction was allowed to react for 30 min at 120 °C prior to the addition of ethanol (30 mL) and sodium borohydride (568 mg, 15 mmol) at ambient temperature. After stirring for overnight, the solution was quenched with water (30 mL) and extracted with diethyl ether (20 mL × 3). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pentane/ethyl acetate = 95:5) to give the title compound as a yellow solid (497 mg, 64%). M.p. 71-73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47-7.50 (several peaks, 4H), 6.64 (dd, *J* = 1.5, 8.5 Hz, 2H), 4.18 (d, *J* = 4.0 Hz, 4H), 2.73 (m, 4H), 2.00 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.6, 140.5, 138.1, 123.4, 117.7, 97.0, 66.4, 24.5, 22.0. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 498. HRMS (TOF MS EI$^+$) m/z calcd for $C_{18}H_{18}O_2Te_2$ [M]$^+$: 525.9431. Found: 525.9434.

Bis(4-Methoxy-3,5-dimethylphenyl) Ditelluride (**10c**). To a solution of 5-bromo-2-methoxy-1,3-dimethylbenzene (860 mg, 4.0 mmol) in anhydrous THF (15 mL) at -78 °C under nitrogen added *tert*-butyllithium(1.7 M, 4.7 mL, 8.0 mmol). After stirring for 1 hour at -78 °C, freshly ground tellurium powder (511 mg, 4.0 mmol) was added and the reaction was allowed to stir for overnight. The reaction mixture was quenched with a saturated ammonium chloride solution (20 mL) and extracted with diethyl ether (30 mL × 3). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pentane/ethyl acetate = 98:2) to give the title compound as a deep red oil (915 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (s, 4H), 3.71 (s, 6H), 2.23 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.7, 138.9, 131.8, 102.0, 59.9, 15.8. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 476. HRMS (TOF MS EI$^+$) m/z calcd for $C_{18}H_{22}O_2Te_2$ [M]$^+$: 529.9744. Found: 529.9746.

***O*-THP-2-Bromo-4-(trifluoromethyl)phenol (11b).** To a solution of 2-bromo-4-(trifluoromethyl)phenol (1.26 g, 5.23 mmol) in dichloromethane (15 mL) were added 3,4-dihydro-2*H*-pyran (0.71 mL, 7.84 mmol) and pyridinium *p*-toluenesulfonate (131 mg, 0.523 mmol). After stirring at room temperature overnight, the reaction mixture was quenched with $NaHCO_3$ (saturated aqueous solution) and extracted with dichloromethane (20 mL × 3). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pentane/ethyl acetate = 100:1) to give the title compound as a pale yellow oil. (1.14 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (m, 1H), 7.51 (m, 1H), 7.22 (dd, *J* = 0.8, 8.8 Hz, 1H), 5.60 (t, *J* = 2.8 Hz, 1H), 3.82 (td, *J* = 3.2, 11.2 Hz, 1H). 3.60-3.65 (several peaks, 1H), 1.98-2.17 (several peaks, 2H), 1.85-1.93 (several peaks, 1H), 1.61-1.80 (several peaks, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.9, 130.4 (q, *J* = 3.8 Hz), 125.7 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 270 Hz), 116.2, 115.6, 112.8, 96.5, 61.8, 29.9, 25.0, 18.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -61.8. HRMS (TOF MS ESI) m/z calcd for $C_{12}H_{12}BrF_3NaO_2$ [M + Na]$^+$: 346.9865. Found: 346.9872.

4-Methoxy-2-(phenyltelluro)phenol (**12a**). *O*-THP-2-bromo-4-methoxyphenol (287 mg, 1.0 mmol), *tert*-butyllithium (1.7 M, 1.2 mL, 2.0 mmol), diphenyl ditelluride (409 mg, 1.0 mmol), *p*-toluensulfonic acid monohydrate (34 mg, 0.18 mmol) were reacted according to general procedure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 95:5) to give the title compound as a yellow solid (131 mg, 40%). M.p. 70-73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (m, 2H), 7.24-7.28 (several peaks, 2H), 7.20 (m, 2H), 6.99 (d, *J* = 9.0 Hz, 1H), 6.89 (dd, *J* = 3.0, 9.0 Hz, 1H), 5.79 (s, 1H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.6, 151.5, 136.3, 129.7, 127.8, 125.1, 118.0, 114.2, 113.7, 103.5, 55.8. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 470. HRMS (TOF MS EI$^+$) m/z calcd for $C_{13}H_{12}O_2Te$ [M]$^+$: 329.9900. Found: 329.9903.

2-(Phenyltelluro)-4-(trifluoromethyl)phenol (**12b**). *O*-THP-2-bromo-4-(trifluoro methyl)phenol (650 mg, 2.0 mmol), *tert*-butyllithium (1.7 M, 2.35 mL, 4.0 mmol), diphenyl ditelluride (818 mg, 2.0 mmol), *p*-toluensulfonic acid monohydrate (68 mg, 0.36 mmol) were reacted according to general procedure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 100:1) to give the title compound as an orange solid (475 mg, 65%). M.p. 43-45 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (m, 1H), 7.54-7.60 (several peaks, 3H), 7.29 (m, 1H), 7.22 (m, 2H), 7.13 (dd, *J* = 0.8, 8.4 Hz, 1H), 6.50 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.1, 138.7 (q, *J* = 3.8 Hz), 136.5, 129.9, 129.5 (q, *J* = 3.8 Hz), 128.3, 123.9 (q, *J* = 33 Hz), 123.7 (q, *J* = 270 Hz), 114.0, 112.9, 103.9. ^{125}Te NMR (126 MHz, $CDCl_3$) δ = 465. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -61.5. HRMS (TOF MS EI$^+$) m/z calcd for $C_{13}H_9F_3OTe$ [M]$^+$: 367.9668. Found: 367.9659.

6-(Phenyltelluro)-2,3-dihydrobenzofuran-5-ol (**12c**). *O*-THP-6-bromo-2,3-dihydrobenzofuran-5-ol (449 mg, 1.5 mmol), *tert*-butyllithium (1.7 M, 1.8 mL, 3.0 mmol), diphenyl ditelluride (614 mg, 1.5 mmol), *p*-toluensulfonic acid monohydrate (57 mg, 0.3 mmol) were reacted according to general procedure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 83:17) to give the title compound as a pale yellow solid (150 mg, 29%). M.p. 118-120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (m, 2H), 7.19 (m, 4H), 6.96 (s, 1H), 5.79 (s, 1H), 4.54 (t, *J* = 7.2 Hz, 2H), 3.22 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 151.7, 136.0, 131.9, 129.6, 127.7, 120.0, 114.0, 110.3, 100.9, 71.3, 30.2. ^{125}Te NMR (126 MHz, $CDCl_3$): δ = 455. HRMS (TOF MS EI$^+$) m/z calcd for $C_{14}H_{12}O_2Te$ [M]$^+$: 341.9900. Found: 341.9890.

6-(Phenyltelluro)-2,3-dihydrobenzofuran-5-ol-*d* (12c-D). A solution of **12c** (34 mg, 0.1 mmol) in deuterochloroform (0.5 mL) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 6.0 mg, 0.15 mmol) in deuterochloroform (0.5 mL) at 0 °C under nitrogen. After stirring for 30 min, the resulting mixture was allowed to warm to ambient temperature, stirred for additional 1h, and treated with

deuterium chloride (35 wt. % in D_2O, 106 mg, 1.0 mmol). The reaction mixture was left for overnight, treated with Mg_2SO_4, and diluted with deuterochloroform (2.0 mL). After filtration, the organic solution was evaporated under reduced pressure, further washed with anhydrous pentane (0.5 mL) and filtered. The filter cake was collected and dried by high-vacuum pump to afford an orange solid (26 mg, 76%). M.p. 101-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (m, 2H), 7.20 (m, 4H), 6.95 (s, 1H), 4.53 (t, *J* = 7.2 Hz, 2H), 3.22 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 151.7, 135.9, 132.0, 129.6, 127.7, 120.1, 114.1, 110.3, 100.9, 71.3, 30.2. ^{125}Te NMR (126 MHz, $CDCl_3$): δ = 452.

HPLC Peroxidation Assay. The experimental setup of an azo-initiated two-phase (water/chlorobenzene) lipid peroxidation model with linoleic acid as oxidizable substrate under atmospheric conditions for determination of R_{inh} and T_{inh} was recently described.[28] The values of R_{inh} and T_{inh} in presence of NAC are reported as means ± SD based on triplicates. The initial concentration of hydroperoxides had been standardized to ca. 175 μM at the beginning of an experiment.

NAC-consumption Assay. The experimental setup for determination of the NAC-concentration in the aqueous phase in a two-phase lipid peroxidation model has been recently described.[13] The values reported are means ± SD based on triplicates.

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Keywords: chain-breaking antioxidant • aryltellurophenol • lipid peroxidation • substituent effect • BDE_{O-H}

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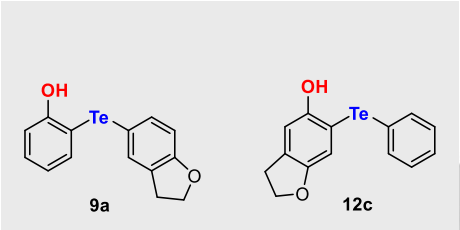
FULL PAPER

Aryltellurophenols outperform α-tocopherol when it comes to regenerability and trapping of lipid peroxyl radicals in a two-phase system. Compounds carrying electron donating substituents in the aryltelluro (**9a**) or phenolic (**12c**) part of the molecule showed the best results.



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Substituent Effects in Chain-Breaking Aryltellurophenol Antioxidants